

(19) World Intellectual Property
Organization
International Bureau



(43) International Publication Date
7 October 2004 (07.10.2004)

PCT

(10) International Publication Number
WO 2004/085058 A1

- (51) International Patent Classification⁷: **B01J 31/02**, 31/28, C07C 29/143, 209/52
- (21) International Application Number: PCT/IB2004/000900
- (22) International Filing Date: 15 March 2004 (15.03.2004)
- (25) Filing Language: English
- (26) Publication Language: English
- (30) Priority Data:
60/457,791 26 March 2003 (26.03.2003) US
60/458,035 27 March 2003 (27.03.2003) US
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- (81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.
- (84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— with international search report

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.



WO 2004/085058 A1

(54) Title: PROCESS TO PRODUCE ENANTIOMERICALLY ENRICHED ALCOHOLS AND AMINES

(57) Abstract: This invention describes a convenient method for the preparation and use of a ruthenium catalyst for a chiral reduction of ketones and imines.

PROCESS TO PRODUCE ENANTIOMERICALLY ENRICHED ALCOHOLS AND AMINES

Background of the Invention

Enantiomerically enriched (chiral) alcohols and amines are important
5 compounds for use as pharmaceutical agents, intermediates for pharmaceutical agents,
polymers, chelating agents, chiral auxiliaries and the like.

Summary of the Invention

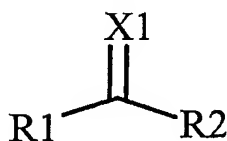
In general, the invention features a convenient method for the preparation and
use of a ruthenium catalyst for a chiral reduction of ketones and imines.

10 In one aspect, the invention provides a method of producing a reducing
catalyst by a) heating a mixture of a ligand, a ruthenium complex, a secondary alcohol
and a tertiary amine; and b) removing the volatile components of the mixture. The
mixture of step a) may be heated to about 30 °C to about 150 °C. The volatile
components of the mixture may be removed under a reduced pressure of between
15 about 0.05 to about 100 mm Hg. The secondary alcohol may be isopropanol.

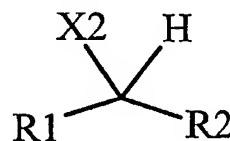
In another aspect, the invention features a method for preparing a reducing
catalyst by a) stirring a mixture of a ligand, a ruthenium complex, and a tertiary amine
in a solvent followed by the addition of a 5:2 molar mixture of formic acid and triethyl
amine. The solvent may include DMF.

20 In another aspect the invention provides a reducing catalyst produced by the
process described above.

In another aspect, the invention features a method for reducing ketones and
imines of Formula I to produce alcohols or amines of Formula 2;



Formula I



Formula 2

25 wherein

R1 and R2 are independently selected from alkyl, alkenyl, cycloalkyl,
heteroalkyl, cycloheteroalkyl, aryl, heteroaryl, substituted aryl and substituted
heteroaryl;

30 R1 and R2 taken together may form a substituted or unsubstituted carbocyclic
or heterocyclic ring of 3 to 12 members;

X1 is O or N-R3

R3 is alkyl, heteroalkyl, cycloalkyl, heteroalkyl, cycloheteroalkyl, aryl, heteroaryl, substituted aryl and substituted heteroaryl;

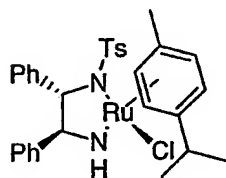
X2 is -OH or -NHR3 where R3 is as defined for Formula I.

- 5 The method includes a) stirring a mixture of a ligand, a ruthenium complex, and a tertiary amine in a solvent followed by the addition of a 5:2 molar mixture of formic acid and triethyl amine; and b) adding the ketone or imine to the mixture.

In another aspect, the method for reducing ketones and imines of Formula I includes a) heating a mixture of a ligand, a ruthenium complex, a secondary alcohol
10 and a tertiary amine; b) removing the volatile components of the mixture; c) adding a solvent to the mixture; and d) adding the ketone or imine to the mixture.

Embodiments of these aspects of the invention may include one or more of the following features. The ligand is N-*p*-toluenesulfonyl-1,2-diphenylethylenediamine. The ruthenium complex is RuCl₂(η 6-*p*-cymene). The tertiary amine is triethyl amine.

- 15 The reducing catalyst is



Advantageously, the present invention contemplates a reduction protocol that
20 benefits from an unexpected solvent effect. In another aspect, this invention provides a simple preparation of the asymmetric reduction catalyst that requires nothing in the way of complex anaerobic, anhydrous manipulation, and produces a catalyst that is at once more reactive and more selective than catalyst prepared as described in the literature.

25 Detailed Description of the Invention

Definitions

In the detailed description, the following definitions are used.

The term leaving group means a substituent which is subject to nucleophilic displacement to form a carbon-carbon or heteroatom-carbon bond as described in

- 30 March, Advanced Organic Chemistry: Reactions, Mechanisms, and Structure,

McGraw-Hill, pp. 251-375, 1968. Examples of leaving groups include, but are not limited to, chloro, bromo, iodo, arylsulfonyl and alkylsulfonyl.

The term "ee" means enantiomeric excess. For instance, one enantiomer of a specific compound is present in a mixture of the enantiomers for that compound at a greater amount relative to the other enantiomer. An enantiomerically enriched form may include a mixture of enantiomers of a specific compound in which the concentration of a single enantiomer of that compound is greater than 50%, more typically greater than 60%, 70%, 80%, or 90%, or higher (e.g., >95%, >97%, >99%, >99.5%), relative to the other enantiomer of that compound.

The term "alkyl," by itself or as part of another substituent, means, unless otherwise stated, a straight or branched chain, or cyclic hydrocarbon radical, or combination thereof, which may be fully saturated, mono- or polyunsaturated and can include di- and multivalent radicals, having the number of carbon atoms designated (i.e. C₁-C₈ means 1-8 eight carbons). Examples of saturated hydrocarbon radicals include, but are not limited to, groups such as methyl, ethyl, n-propyl, isopropyl, n-butyl, t-butyl, isobutyl, sec-butyl, cyclohexyl, (cyclohexyl)ethyl, cyclopropylmethyl, homologs and isomers of, for example, n-pentyl, n-hexyl, n-heptyl, n-octyl, and the like. An unsaturated alkyl group is one having one or more double bonds or triple bonds. Examples of unsaturated alkyl groups include, but are not limited to, vinyl, 2-propenyl, crotyl, 2-isopentenyl, 2-(butadienyl), 2,4-pentadienyl, 3-(1,4-pentadienyl), ethynyl, 1- and 3-propynyl, 3-butynyl, and the higher homologs and isomers. The term "alkene" by itself or as part of another substituent means a divalent radical derived from an alkane, as exemplified by -CH₂CH₂CH₂CH₂-. A "lower alkyl" or "lower alkene" is a shorter chain alkyl or alkene group, having eight or fewer carbon atoms.

The terms "alkoxy..... alkylamino" and "alkylthio" refer to those groups having an alkyl group attached to the remainder of the molecule through an oxygen, nitrogen or sulfur atom, respectively. Similarly, the term "dialkylamino" is used in a conventional sense to refer to -NR'R" wherein the R groups can be the same or different alkyl groups.

The term "heteroalkyl," by itself or in combination with another term, means, unless otherwise stated, a stable straight or branched chain, or cyclic hydrocarbon radical, or combinations thereof, fully saturated or containing from 1 to 3 degrees of

unsaturation, consisting of the stated number of carbon atoms and from one to three heteroatoms selected from the group consisting of O, N, and S, and wherein the nitrogen and sulfur atoms may optionally be oxidized and the nitrogen heteroatom may optionally be quaternized. The heteroatom(s) O, N and S may be placed at any interior position of the heteroalkyl group. Examples include, but are not limited to, -CH₂-CH₂-O-CH₃, -CH₂-CH₂-NH-CH₃, -CH₂-CH₂-N(CH₃)-CH₃, -CH₂-S-CH₂-CH₃, -CH₂-CH₂-S(O)-CH₃, -CH₂-CH₂-S(O)₂-CH₃, -CH=CH-O-CH₃, -Si(CH₃)₃, -CH₂-CH=N-OCH₃, and -CH=CH-N(CH₃)-CH₃. Up to two heteroatoms may be consecutive, such as, for example, -CH₂-NH-OCH₃. Also included in the term "heteroalkyl" are those radicals described in more detail below as "heterocycloalkyl." The terms "cycloalkyl" and "heterocycloalkyl", by themselves or in combination with other terms, represent, unless otherwise stated, cyclic versions of "alkyl" and "heteroalkyl", respectively. Additionally, for heterocycloalkyl, a heteroatom can occupy the position at which the heterocycle is attached to the remainder of the molecule. Examples of cycloalkyl include, but are not limited to, cyclopentyl, cyclohexyl, 1-cyclohexenyl, 3-cyclohexenyl, cycloheptyl, and the like. Examples of heterocycloalkyl include, but are not limited to, 1-piperidinyl, 2-piperidinyl, 3-piperidinyl, 4-morpholinyl, 3-morpholinyl, tetrahydrofuran-2-yl, tetrahydrofuran-3-yl, tetrahydrothien-2-yl, tetrahydrothien-3-yl, 1-piperazinyl, 2-piperazinyl, and the like.

The terms "halo" or "halogen," by themselves or as part of another substituent, mean, unless otherwise stated, a fluorine, chlorine, bromine, or iodine atom. Additionally, terms such as "Fluoroalkyl," are meant to include monofluoroalkyl and polyfluoroalkyl.

The term "aryl," employed alone or in combination with other terms (e.g., aryloxy, arylthioxy, aralkyl) means, unless otherwise stated, an aromatic substituent which can be a single ring or multiple rings (up to three rings) which are fused together or linked covalently. The term "heteroaryl" is meant to include those aryl rings which contain from zero to four heteroatoms selected from N, O, and S, wherein the nitrogen and sulfur atoms are optionally oxidized, and the nitrogen atom(s) are optionally quaternized. The "heteroaryl" groups can be attached to the remainder of the molecule through a heteroatom. Non-limiting examples of aryl and heteroaryl groups include, but are not limited to, phenyl, 1-naphthyl, 2-naphthyl, 4-biphenyl, 1-pyrrolyl, 2-pyrrolyl, 3-pyrrolyl, 3-pyrazolyl, 2-imidazolyl, 4-imidazolyl, pyrazinyl, 2-

oxazolyl, 4-oxazolyl, 2-phenyl-4-oxazolyl, 5-oxazolyl, 3-isoxazolyl, 4-isoxazolyl, 5-isoxazolyl, 2-thiazolyl, 4-thiazolyl, 5-thiazolyl, 2-furyl, 3-furyl, 2-thienyl, 3-thienyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-pyrimidyl, 4-pyrimidyl, 5-benzothiazolyl, purinyl, 2-benzimidazolyl, 1-indolyl, 5-indolyl, 1-isoquinolyl, 5-isoquinolyl, 2-quinoxaliny, 5-quinoxaliny, 3-quinolyl, and 6-quinolyl.

Substituents for each of the above noted aryl ring systems are selected from the group of acceptable substituents described below. The term "aralkyl" is meant to include those radicals in which an aryl or heteroaryl group is attached to an alkyl group (e.g., benzyl, phenethyl, pyridylmethyl and the like) or a heteroalkyl group (e.g., phenoxymethyl, 2-pyridyloxymethyl, 3-(1-naphthyloxy)propyl, and the like). Each of the above terms (e.g., "alkyl.... heteroalkyl" and "aryl") are meant to include both substituted and unsubstituted forms of the indicated radical. Preferred substituents for each type of radical are provided below.

Substituents for the alkyl and heteroalkyl radicals (including those groups often referred to as alkylene, alkenyl, heteroalkylene, heteroalkenyl, alkynyl, cycloalkyl, heterocycloalkyl, cycloalkenyl, and heterocycloalkenyl) can be a variety of groups selected from: -OR', =O, =NR', =N-OR', -NR'R", -SR', -halogen, -SiR'R"R, -OC(O)R', -C(O)R', -CO₂R', CONR'R", -OC(O)NR'R", -NR'C(O)R', -NR'C(O)NR'R", -NR'COOR", -NH-C(NH₂)=NH, -NR'C(NH₂)=N-H, -NH-C(NH₂)=NR', -S(O)R', S(O)₂R', -S(O)₂NR'R", -CN and -NO₂ in a number ranging from zero to (2N+1), where N is the total number of carbon atoms in such radical. R', R" and X" each independently refer to hydrogen, unsubstituted C1-COalkyl and heteroalkyl, unsubstituted aryl, aryl substituted with 1-3 halogens, unsubstituted alkyl, alkoxy or thioalkoxy groups, or aryl-(C1-C4)alkyl groups. When R' and R" are attached to the same nitrogen atom, they can be combined with the nitrogen atom to form a 3-7 membered ring. For example, -NR'R" is meant to include 1-pyrrolidinyl and 4-morpholinyl. From the above discussion of substituents, one of skill in the art will understand that the term "alkyl" is meant to include groups such as haloalkyl (e.g., -CF₃ and -CH₂CF₃) and acyl (e.g., -C(O)CH₃, -C(O)CF₃, -C(O)CH₂OCH₃, and the like).

Similarly, substituents for the aryl groups are varied and are selected from: halogen, -OR, -OC(O)R, -NR'R", -SR, -R', -CN, -NO₂, -CO₂R', -CONR'R', -C(O)R', -OC(O)NR'R", -NR'C(O)R', -NR'C(O)₂R', -NR'-C(O)NR'R", -NH-C(NH₂)=NH, -

NR'C(NH₂)=NH, -NH-C(NH₂)=NR', -S(O)R', -S(O)₂R', -S(O)₂NR'R'', -N₃, -CH(Ph)₂, perfluoro(C1-C4)alkoxy, and perfluoro(C1-C4)alkyl, in a number ranging from zero to the total number of open valences on the aromatic ring system; and where R', R'' and R''' are independently selected from hydrogen, (C1-C8)alkyl and heteroalkyl,
 5 unsubstituted aryl, (unsubstituted aryl)-(C1-C4)alkyl, and (unsubstituted aryloxy-(C1-C4)alkyl.

Two of the substituents on adjacent atoms of the aryl ring may optionally be replaced with a substituent of the formula -S-C(O)-(CH₂)_q-R-, wherein S and R are independently -NH-, -O-, -CH₂- or a single bond, and the subscript q is an integer of
 10 from 0 to 2. Alternatively, two of the substituents on adjacent atoms of the aryl ring may optionally be replaced with a substituent of the formula -A-(CH₂)_w-B-, wherein A and B are independently -CH₂-, -O-, -NH-, -S-, -S(O)-, -S(O)₂-, -S(O)₂NR'- or a single bond, and w is an integer of from 1 to 3. One of the single bonds of the new ring so formed may optionally be replaced with a double bond. Alternatively, two of the
 15 substituents on adjacent atoms of the aryl ring may optionally be replaced with a substituent of the formula -(CH₂)_w-G-(CH₂)_{w'}-, where w and w' are independently integers of from 0 to 3, and G is -O-, -NR'-, -S-, -S(O)-, -S(O)₂-, or -S(O)₂NR'-. The substituent R' in -NR'- and -S(O)₂NR'- is selected from hydrogen or unsubstituted (C1-C6)alkyl. As used herein, the term "heteroatom" is meant to include oxygen (O),
 20 nitrogen (N),) and sulfur(S).

Description of the Invention

In one aspect, the present invention contemplates a general reduction protocol that benefits from a heretofore unappreciated solvent effect. In another aspect, this invention provides a simple preparation of the asymmetric reduction catalyst that
 25 requires nothing in the way of complex anaerobic, anhydrous manipulation, and produces a catalyst that is at once more reactive and more selective than catalyst prepared as described in the literature.

Methods for achieving the chiral reduction of ketones and imines include enantioselective hydride reduction, enantioselective hydrogenation and
 30 enantioselective transfer hydrogenation (see for example Palmer, M.J; et.al., Tetrahedron: Asymmetry, (1999), 10, 2045 and references cited therein).

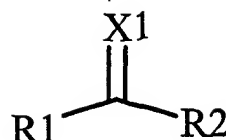
In another aspect of this invention, the ketone A is reduced by enantioselective transfer hydrogenation using a modification of the method described by Noyori, et.al.

(Noyori, R.; Hashiguchi, S., *Accts. Chem. Res.*, (1997), 30, 97-102; Fujii, A.; Hashiguchi, S.; Uematsu, N.; Ikariya, T.; Noyori, R., *J. Am. Chem. Soc.* (1996), 118, 2521-2522). The modifications obviate the laborious chiral catalyst preparation and recrystallization as described by Noyori and others (Vedejs, E., et.al., *J. Org. Chem.* 5 (1999), 64, 6724), and provides a simple, oxygen insensitive, catalyst preparation which enables the preparation of a variety of alcohols of Formula 2. The catalyst can be prepared in advance and stored for a period of time without degradation in its performance. The present method also benefits from a heretofore unappreciated solvent effect. The use of a polar solvent such as dimethylformamide, as compared to 10 THF and methylene chloride, provides elevated yields in shorter time (48 hours reduced to 45 minutes) and with significantly improved enantioselection (ca. 60%ee improved to >99%ee).

In preparing the catalyst, a mixture of a suitable ligand such as *N*-tosyl-1,2-diphenylethylenediamine and a suitable source of ruthenium complex such as 15 $\text{RuCl}_2(\eta^6\text{-}p\text{-cymene})$ dimer in a suitable secondary solvent alcohol such as isopropanol, 2-butanol, cyclohexanol and the like containing a suitable tertiary amine such as triethylamine is heated between about 60-80°C for 1 hour. Evaporation of the solvent gives the desired catalyst as a stable orange-brown solid (Method A).

Alternatively, the catalyst can be prepared by combining the ligand, *N*-tosyl- 20 1,2-diphenylethylenediamine and a ruthenium source such as $\text{RuCl}_2(\eta^6\text{-}p\text{-cymene})$ dimer, in DMF, either DMF only or in the presence of a co-solvent such as methyl-*tert*-butyl ether (MTBE), followed by the addition of a 5:2 mixture (mole/mole) of formic acid and triethyl amine (Method B). If the reduction is being conducted by the preparation of the catalyst by Method A, the reduction is completed by the addition of 25 polar solvent to the catalyst followed by a ketone of Formula A and a 5:2 to 1:1 (mole/mole) mixture of formic acid and triethylamine and stirring the mixture for about 45 minutes to about 6 hours, usually 45 minutes, at a temperature between about -15°C to room temperature, usually room temperature, and at a pressure between about 20mmHg to 1 atm.

30 This invention then, describes a novel catalyst and process for the reduction of ketones and imines of Formula I;



Formula I

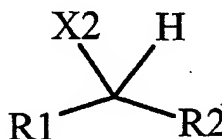
wherein R1 and R2 are independently selected from alkyl, alkenyl, cycloalkyl,
 5 heteroalkyl, cycloheteroalkyl, aryl, heteroaryl, substituted aryl and substituted heteroaryl;

X1 is O or N-R3

wherein R3 is alkyl, heteroalkyl, cycloalkyl, heteroalkyl, cycloheteroalkyl, aryl,
 heteroaryl, substituted aryl and substituted heteroaryl;

10 R1 and R2 taken together may form a substituted or unsubstituted carbocyclic or heterocyclic ring of 3 to 12 members;

to give alcohols or amines of Formula 2



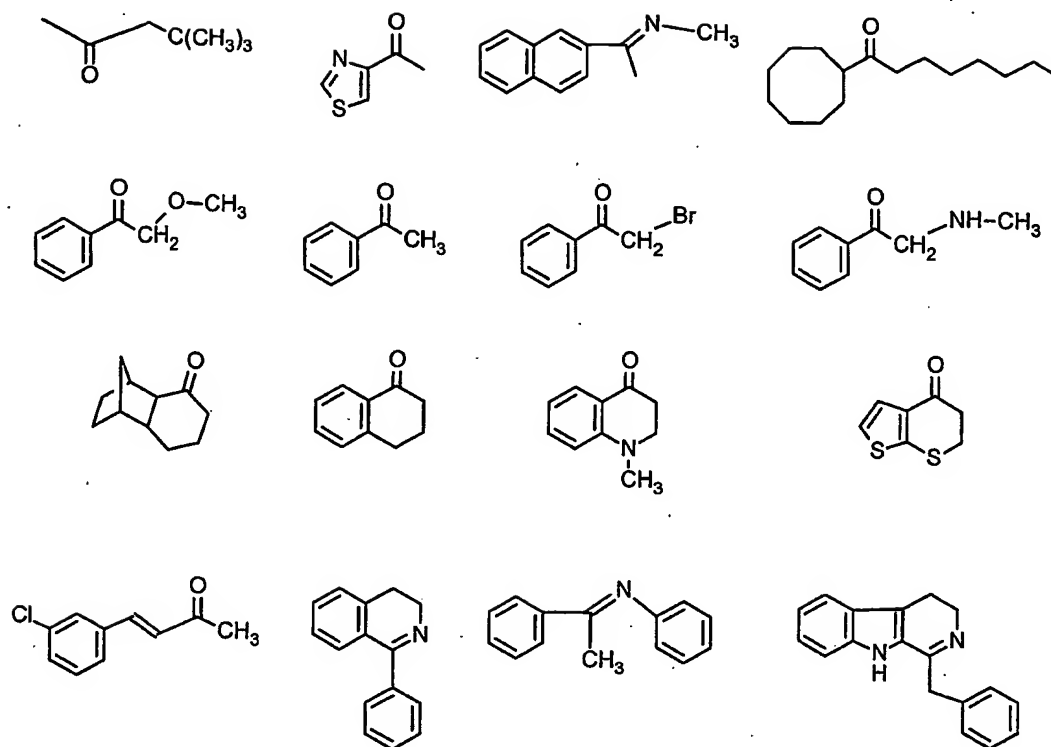
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Formula 2

wherein R1 and R2 are as described for Formula I;

X2 is -OH or -NHR3 where R3 is as defined for Formula I.

Examples of ketones and imines which may be reduced to the corresponding
 20 chiral alcohol or amine are shown in Table 1. The examples are illustrative only and not intended to limit the scope of reductions which may be carried out.



5 Examples

Example 1: Preparation of catalyst- Method A

[RuCl₂(η⁶-*p*-cymene)]₂ (0.84g, 1.37mmol), Et₃N (0.67g, 6.66mmol, 0.93mL), and
 10 (1*S*, 2*S*)-*N*-*p*-toluenesulfonyl-1,2-diphenylethylenediamine (1.0g, 2.72mmol,
 1.78mol% based upon ketone) are combined in a 500mL 1N round bottom flask.
 Isopropanol (25 mL) and Et₃N (0.67g, 6.66mmol, 0.93mL) are added, a reflux
 condenser is attached and the mixture is warmed under reflux for 1 hour. The mixture
 is cooled to room temperature and concentrated *in vacuo* to furnish the catalyst as a
 15 brown powdery solid.

Example 2: Reduction of 2-chloroacetyl pyridine



To the catalyst prepared in example 1 is added anhydrous DMF (Aldrich Sure Seal,
 20 225mL), followed in order by 2-chloroacetylpyridine (23.88g, 0.153mol) and
 HCOOH/Et₃N (5:2, Fluka, 55mL). After ca. 2-3 minutes of stirring (room

temperature) bubbles are apparent, emanating from the stirring vortex of the red-black solution. Reaction progress is monitored by reverse phase analytical HPLC, and after 75 minutes of stirring, the starting material had been consumed (95:5 NaH₂PO₄/H₃PO₄ buffered water/CH₃CN to 5:95, 17 minutes; retention time of starting chloroketone: 7.39 minutes, retention time of halohydrin 2.66 minutes). The reaction is quenched by adding MeOH (25mL) and stirred 5 minutes. The solvents are removed *in vacuo* (cold finger rotovapor, vacuum pump) to give a red-black viscous oil. The crude material is taken up in Et₂O/CH₂Cl₂ (4:1, 1.25L), placed in a 3L separatory funnel, wash with saturated aq. NaHCO₃ (1.0L), brine (1.0L), and dried (Na₂SO₄). Filtration and concentration *in vacuo* afforded the crude product as a red-orange oil which is purified by chromatography on a column of silica gel (70mm OD, 250g 230-400mesh, packed hexanes; compound applied in CH₂Cl₂/hexanes 60:40; eluted with hexanes/Et₂O (75:25 2L; 65:35 2L; 55:45 2L; 350mL fractions). Fractions 9-16 are combined to afford 14.72g (61%) of the halohydrin as pale yellow solid.

Physical Characteristics: MP: 47-48°C; ¹H-NMR (400MHz, CDCl₃): δ = 8.65, 7.92, 7.58, 7.44, 5.13, 4.60, 3.91; IR (neat): 3138, 3074, 3029, 3014, 2974, 2964, 2955, 2895, 2862, 2848, 2472, 2350, 2328, 2305, 2261 (w), cm⁻¹; Anal. Found: C, 53.23; H, 5.12; N, 8.82; **Specific Rotation** [α]_D²⁵ = -39 (c 0.94, CH₂Cl₂). **Chiral HPLC Analysis** (Chiracel OJ): 98:2; 96%ee.

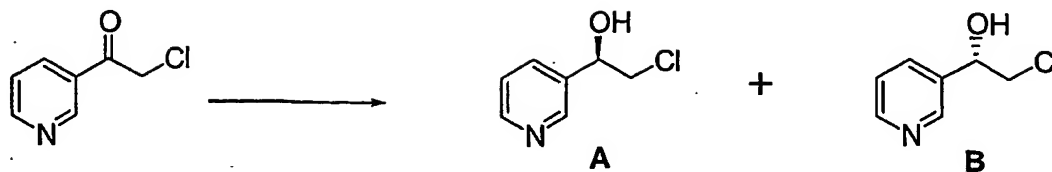
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Example 3: Analysis of optical purity by chiral column chromatography

Analysis of the optical purity of *R*-2-(1-hydroxy-2-chloroethyl)-pyridine: analysis is performed on a 0.46X25CM Chiracel OJ column connected to a Gilson-Ranin HPLC system; with a solvent consisting of 2.5% *i*-PrOH in heptane, pumping at 0.5mL/minute. The compound in question, as a solution in CH₂Cl₂ is injected (10μL) at time = 0 and the UV detector is set at 220nm. At time = 45.23 minutes a peak with an integrated area of 98area% is detected; at time = 47.77 a peak with an integrated area of 2area% is detected, representative of a 98:2 ratio, 96%ee.

Example 4: Demonstration of Solvent Effect.

Table 2 summarizes the results of reducing 3-chloroacetylpyridine. The reductions are conducted according to the procedure of Example 1 with the exception that solvent and pressure are varied as listed in the Table.



Et ₃ N/HCOOH + Solvent	Time	Overall Yield(%)	Ratio of A/B	Pressure (mm Hg)
None	48h	27	80/20	atm
CH ₂ Cl ₂	16h	39	85:15	atm
THF	16h	37	83:17	atm
DMF	16h	67	95/5	atm
DMF	0.75h	80	100/0	40

5

Table 2

Example 5: Reduction of 2-chloroacetylfuran to *S*-1-(2-furyl)-2-chloroethanol

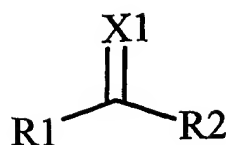
- 10 [RuCl₂(η⁶-*p*-cymene)]₂ (0.99g, 1.61mmol), Et₃N (0.67g, 6.66mmol, 0.93mL), and (1*R*, 2*R*)-*N*-*p*-toluenesulfonyl-1,2-diphenylethylenediamine (1.18g, 3.22mmol, 2.25mol% based upon ketone) are combined in a 500mL 1N round bottom flask. *i*-PrOH (25 mL) and Et₃N (0.67g, 6.66mmol, 0.93mL) are added, a reflux condenser is attached and the mixture is warmed under reflux, and maintained, for 1 hour. Cool to
- 15 room temperature and concentrate *in vacuo* (rotovapor) to furnish the catalyst as an orange-brown powdery solid. To the catalyst is added anhydrous DMF (Aldrich Sure Seal, 250mL), followed in order by 2-chloroacetylfuran (20.6g, 0.143mol) and HCOOH/Et₃N (5:2, Fluka, 51mL). After ca. 2-3 minutes of stirring (room temperature) bubbles (presumed to be CO₂) are apparent, emanating from the stirring
- 20 vortex of the red-black solution. Reaction progress is monitored by reverse phase analytical HPLC, and after 65 minutes of stirring, the starting material had been consumed (95:5 NaH₂PO₄/H₃PO₄ buffered water/CH₃CN to 5:95, 17 minutes;

retention time of starting chloroketone: 6.70 minutes, retention time of halohydrin 6.35 minutes). Quench the reaction by adding MeOH (25mL), stir 5 minutes and then the reaction mixture is poured into ice-water (1L) and the aqueous phase is saturated with salt. The mixture is transferred to a 2L separatory funnel with ether (500mL),
5 shaken, and the organic phase is removed. The aqueous layer is extracted with ether (3X250mL) and the combined organic layers are wash with saturated aq. NaHCO₃ (0.5L), brine (4X250mL), and dried (Na₂SO₄). Filtration and concentration *in vacuo* afforded the crude product as a red-orange oil (20.5g) that is triturated with ether/pentane (10:90, 4X 100mL). The combined triturates are concentrated *in vacuo*
10 (take care as the halohydrin is volatile, hence the choice of ether/pentane as tritulant and no removal of DMF *in vacuo*) to furnish the desired halohydrin (15.97g, 76%) in good purity as determined by HPLC and ¹H-NMR. **Physical Characteristics:** ¹H-NMR (400MHz, CDCl₃): δ = 7.41, 6.37, 4.95, 3.85, 2.58; IR (diffuse reflectance) 1428, 1422, 1221, 1205, 1198, 1166, 1096, 1021, 953, 924, 883, 789, 738, 714, 666,
15 cm⁻¹; MS (EI) m/z (rel. intensity) 146 (17), 129 (2), 98 (6), 97 (base), 95 (3), 94 (1), 69 (3), 41 (2); HRMS (EI) found 146.0136; Specific Rotation $[\alpha]_{25}^D = 17$ (c 0.97, methanol); Chiral HPLC Analysis (Chiracel OJ): 99:1; 98%ee.

Example 6. Reduction of 2-chloroacetyl pyridine (Catalyst Preparation Method B)
20 (1*R*, 2*R*)-*N*-*p*-toluenesulfonyl-1,2-diphenylethylenediamine (1.103g, 3.01mmol), [RuCl₂(η^6 -*p*-cymene)]₂ (0.936g, 1.528mmol), and triethylamine (0.072g, 0.71mmol) in 5ml DMF are combined in a 50ml 3-neck round bottom flask. The mixture is allowed to stir for 1hr at room temperature, then a solution of 2-chloroacetyl pyridine (3.7g, 19.7mmol) in MTBE (15mL) is added in one portion and
25 the flask is rinsed with DMF (10mL) which is added to the reaction vessel. A gentle flow of nitrogen (~5ml/ second) is then initiated and bubbled through the reaction mixture. To this solution is added 8.06mL of a 5:2 (mole/mole) mixture of formic acid/triethyl amine in one portion. An endotherm is observed over the next 30 min with the temp dropping from 22°C to 12°C. The mixture is stirred for 1hr @ RT.
30 HPLC (3 drops reaction diluted in 1ml methanol) showed no detectable 2-chloroacetyl pyridine (RT = 5.4 min) and 97.5 area% *S*-2-(1-hydroxy-2-chloroethyl)-pyridine (RT = 3.40 min) (Agilent HPLC 50:50 acetonitrile: 0.1M NH₄OAc, 1ml/min, detection at 254 nm, 250 X 4.6 mm Zorbax RX-C8).

We Claim:

1. A method of producing a reducing catalyst, comprising
 - a) heating a mixture of a ligand, a ruthenium complex, a secondary alcohol and a tertiary amine; and
 - 5 b) removing the volatile components of the mixture.
2. The method of claim 1, wherein the mixture of step a is heated to about 30 °C to about 150 °C.
- 10 3. The method of claim 1, wherein the volatile components of the mixture are removed under a reduced pressure of between about 0.05 to about 100 mm Hg.
4. The method of claim 1, wherein the secondary alcohol is isopropanol.
- 15 5. A method for preparing a reducing catalyst, comprising
 - a) stirring a mixture of a ligand, a ruthenium complex, and a tertiary amine in a solvent followed by the addition of a 5:2 molar mixture of formic acid and triethyl amine.
- 20 6. The method of claim 5, wherein the solvent comprises DMF.
7. The method of claims 1 or 5, wherein the ligand is N-*p*-toluenesulfonyl-1,2-diphenylethylenediamine.
- 25 8. The method of claims 1 or 5, wherein the ruthenium complex is RuCl₂(η⁶-*p*-cymene).
9. The method of claims 1 or 5, wherein the tertiary amine is triethyl amine.
- 30 10. A reducing catalyst produced by the process of claim 1 or 5.
11. A method for reducing ketones and imines of Formula I;



Formula I

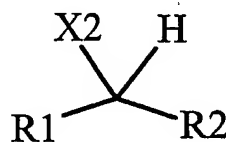
wherein R1 and R2 are independently selected from alkyl, alkenyl, cycloalkyl, heteroalkyl, cycloheteroalkyl, aryl, heteroaryl, substituted aryl and substituted heteroaryl;

X1 is O or N-R3

wherein R3 is alkyl, heteroalkyl, cycloalkyl, heteroalkyl, cycloheteroalkyl, aryl, heteroaryl, substituted aryl and substituted heteroaryl;

R1 and R2 taken together may form a substituted or unsubstituted carbocyclic or heterocyclic ring of 3 to 12 members;

to produce alcohols or amines of Formula 2



Formula 2

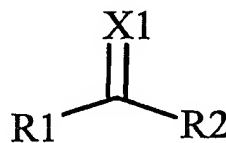
wherein R1 and R2 are as described for Formula I;

X2 is -OH or -NHR3 where R3 is as defined for Formula I;

comprising

- a) stirring a mixture of a ligand, a ruthenium complex, and a tertiary amine in a solvent followed by the addition of a 5:2 molar mixture of formic acid and triethyl amine; and
- b) adding the ketone or imine to the mixture.

12. A method for reducing ketones and imines of Formula I;



Formula I

wherein R1 and R2 are independently selected from alkyl, alkenyl, cycloalkyl, heteroalkyl, cycloheteroalkyl, aryl, heteroaryl, substituted aryl and substituted heteroaryl;

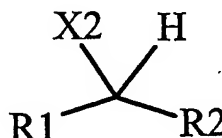
X1 is O or N-R3

- 5 wherein R3 is alkyl, heteroalkyl, cycloalkyl, heteroalkyl, cycloheteroalkyl, aryl, heteroaryl, substituted aryl and substituted heteroaryl;

R1 and R2 taken together may form a substituted or unsubstituted carbocyclic or heterocyclic ring of 3 to 12 members;

to produce alcohols or amines of Formula 2

10



Formula 2

wherein R1 and R2 are as described for Formula I;

- 15 X2 is -OH or -NHR3 where R3 is as defined for Formula I;

comprising

- a) heating a mixture of a ligand, a ruthenium complex, a secondary alcohol and a tertiary amine;
- b) removing the volatile components of the mixture;
- 20 c) adding a solvent to the mixture; and
- d) adding the ketone or imine to the mixture.

13. The method of claim 11 or 12, wherein the solvent comprises DMF.

- 25 14. The method of claim 11 or 12, wherein the ligand is N-*p*-toluenesulfonyl-1,2-diphenylethylenediamine.

15. The method of claim 11 or 12, wherein the ruthenium complex is RuCl₂(η⁶-*p*-cymene).

30

INTERNATIONAL SEARCH REPORT

Int. Application No
PCT/IB2004/000900

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 B01J31/02 B01J31/28 C07C29/143 C07C209/52

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 B01J C07C

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	NOYORI ET AL: "Ruthenium(II)-Catalyzed Asymmetric Transfer Hydrogenation of Ketones Using a Formic Acid-Triethylamine Mixture" J. AM. CHEM. SOC., vol. 118, pages 2521-2522, XP002284861 cited in the application page 2521, column 1, paragraph 2 -column 2, paragraph 1 -/-	1-5, 7-12, 14, 15

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

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Date of the actual completion of the international search

17 June 2004

Date of mailing of the international search report

13/07/2004

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INTERNATIONAL SEARCH REPORT

Int. Patent Application No
PCT/IB2004/000900

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	VEDEFS: "Substituted Isoquinolines by Noyori Transfer Hydrogenation: Enantioselective Synthesis of Chiral Diamines Containing an Aniline Subunit" J. ORG. CHEM., vol. 64, 1999, pages 6724-6729, XP002284862 cited in the application page 6726, column 1, paragraph 3 -----	1-5, 7-12,14, 15
X	NOYORI: "The Catalyst Precursor, Catalyst and Intermediate in the Ru (II)-Promoted Asymmetric Hydrogen Transfer between Alcohols and Ketones" ANGEW. CHEM. INT. ED., vol. 36, no. 3, 1997, pages 285-288, XP002284863 page 287, column 1, paragraph 4 -----	1-4,8-10
P,X	WO 2004/014551 A (JOHNSON MATTHEY PLC ;CHEN WEIPING (GB); XIAO JIANLIANG (GB); HEMS) 19 February 2004 (2004-02-19) page 12, paragraph 4 -page 13, paragraph 1 -----	1-15

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